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EXAMINER	
LIU, SAMUEL W	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 03/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

HC

Office Action Summary	Application No.	Applicant(s)	
	10/030,137	STOTT, KELVIN	
	Examiner	Art Unit	
	Samuel W Liu	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28 and 43* is/are pending in the application.

4a) Of the above claim(s) *none* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-28 and 43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action previously mailed 28 December 2004 is vacated in favor of the following non-final action because mailed was a draft of the office action thereof.

Status of the claims

Claims 1-28 and 43 are pending.

Applicants' amendment filed 18 October 2004, which cancels claims 29-42 and 44-45, and amends claims 1-28 has been entered. Also, applicants' request for extension of time of one month (filed 18 October 2004) has been entered. The following Office action is applied to the pending claims 1-28 and 43.

Please note that the objection(s) and/or rejection(s) not explicitly stated and/or restated below are withdrawn.

IDS

The references of IDS filed 18 October 2004 have been considered by Examiner.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 1-28 and 43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 phrase "*favorable non-covalent interactions*" is not apparent because the specification does not define it; does "favorable" refers to stable or preferable or certain types of

non-covalent interactions, e.g., van de Waals force, or/and hydrogen bonding or/and ionic interaction? See also claim 27. The dependent claims are also rejected.

Claim 2 is indefinite because the claim set forth total at least six amino acids (2 for Nα-substituted residues and 4 ("more than three") for Nα-unsubstituted ones. Yet, the said β-strand forming section of claim 1 from which claim 2 depends set forth that the section has four residues.

The applicant's response to the rejection under 35 USC 112, second paragraph

On page 35, the response filed 18 October 2004 argues that claim 18 recitation "a mimic thereof" is clear as the specification defines what "peptide mimic" is (page 9, the last paragraph). The applicants' argument is found to be unpersuasive because the issue here is not clarity of the phrase peptide mimic *per se* but the issue regarding whether or not the "mimic" refers to the mimic of the claimed compound, or the mimic of the sequence consisting of 7 amino acids (see line 4 of the claim).

Claim Rejections - 35 USC §102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1, 4-13, 15-18 and 22-28 are rejected under 35 U.S.C. 102(b) as being anticipated by Quibell M. et al. (*J. Chem. Soc. Perkin. Trans* (1995) 1, 2019-2024), as is evidenced by the known facts (i)"KLVFF" is a consensus sequence contributed to β-strand interaction taught by Tjernberg, L. O. et al. (*J. Biol. Chem.* (1997) 272, 12601-12605, from IDS filed 10/18/04); and (ii) proteolysis-resistance is an inherent property of the Nα-substituted polypeptide, which is disclosed by Miller S. M. et al. (*Drug Dev. Res.* (1995) 35, 20-32).

Quibell et al. teach a peptide compound comprising (*i*) a peptide portion (residues 16-33) that is capable of forming β-structure on its *N-terminal* section (*equivalent to the first edge of the instant application*) wherein "KLVFF" (residues 16-20, depicted in the polypeptide sequence on page 2020) is a β-strand forming **core** sequence, and, wherein Phenylalanine residue (F) 20 is Nα-substituted with N-(2-hydroxy-4-methoxybenzyl), *i.e.*, Hmb), and (*ii*) a peptide portion (residues 34-42) located at the C-terminal section of the polypeptide (*equivalent to the second edge of the instant application*) wherein residues 34-36 and 39-42 participate in β-strand interaction as depicted in Figure 1 (*see especially "cross "X" symbol which indicates intermolecular β-strand interaction*). The Quibell's polypeptide has the following characteristics: (1) comprises at least four consecutive α-L-amino acid residues (e.g., "KLVFF"

motif) which are able to form non-covalent interaction with neighboring side chains of the target β-strand (e.g., other amyloid β-strand molecule) as is evidenced by Tjernberg et al. reference; and, (2) within KLVFF (residues 16-20), there is one Nα-substituent (i.e., Phe 20). Note that the β-amyloid polypeptides have prone of forming interchain β-strand interaction, and the "KLVFF" motif resides in the β-amyloid. There therefore exists interaction between the target β-strand and the β-strand forming section of the peptide (see "... *substantial improvement in the quality of the β-amyloid (1-43) crude product*" on page 2020, the left column, the 2nd paragraph of the Quibell's reference). Thus, the above Quibell's teachings anticipate the instant claims 1 and 15.

The Quibell's peptide compound is made for preventing hydrogen boding between β-structures of individual polypeptides (i.e., interchain interaction) thereby inhibiting intermolecular aggregation of the said polypeptides (see page 2019). The Hmb-modified β-amyloid (consisting of 34 residues) promotes formation a β-strand and hinds the β-amyloid aggregation (see the above statement). The above Quibell's teachings anticipate the instant claims 4 and 7.

Since proteolysis-resistance is an inherent property of the Nα-substituted polypeptide, and since the Quibell's composition is such the polypeptide, the above teachings anticipate the instant claim 5.

Since claim 6 recites the limitation that the Nα-substituted group is "a group that is connected to the Nα atom by a CH_2 (methylene) group", and since the Quibell's peptide compound contains CH_2– group in N-(2-hydroxy-4-methoxybenzyl) wherein said CH_2– group is

linked to Nα atom of peptide backbone (see structure depicted on page 2019), the above Quibell's teachings anticipate the instant claim 6.

In the "KLVFF" motif, residues Leu, Val, and Phe have β-sheet formation propensity > 1.00, which anticipates the instant claim 8.

Quibell et al. teach that their β-forming peptide comprising the "KLVFF" motif has amino acid side chains that promote β-structure formation, e.g., 3-methylvaleric group (Leu), isovaleric group (Val), methyl group (Ala) and 3-methylvaleric group (Ile); these groups have hydrophobic characters and high propensity of forming β-structure. The Quibell's teaching anticipates the instant claims 9-10.

Quibell et al. teach that the β-strand forming peptide contains glycine residues (see page 2020 and Figure 1) which hinder the β-strand stacking as glycine has no said chain, which anticipates the instant claim 11.

In the patent claim 3, Kelly teaches interstrand interaction via side chains of the polypeptide forming β-strands, which anticipates the instant claim 12.

In "*Results and Discussion*" section, Quibell et al. teach the β-forming peptide comprising Hmb-substituents is detected and analyzed by HPLC-assisted electrospray mass spectrometry (see page 2020, the left column), wherein the Hma group gives rise to a characteristic peak in the mass spectrometric profile (see Figure 2). Thus, the Quibell's teaching anticipates the instant claim 13.

Quibell et al. teach that the Nα-substituted (Hmb-modified) polypeptide inhibits aggregation of β-amyloid (i.e., Alzheimer's Aβ peptide); the Quibell's polypeptide comprises "KLVFFAE" (see peptide structure in page 2020). Because the inhibition requires the

polypeptide direct interaction with target β-strand (i.e., the Aβ peptide), the Quibell's teaching anticipates the instant claims 16-17.

The sequence "KLVFFAE" (residues 16-22) of the Quibell's polypeptide meets all the limitations set forth in claim 18.

The N-terminus of the Quibell's peptide is unmodified, i.e., comprises free N- and C-termini, which anticipates the instant claim 22.

In Figure 1 (*a*), the Quibell's polypeptide is attached to a resin, which anticipates the instant claims 23-24 (note that claim 24 sets forth the limitation that the functional component is a resin).

Quibell et al. teach that their polypeptide attached to the resin through C-terminus of the polypeptide, which anticipates the instant claim 25.

Since the Hmb-substituted polypeptide is able to associate with β-amyloid (target β-strand) which comprises "KLVFF", the above Quibell's teaching anticipates the instant claim 26.

Further, Quibell et al. teach that, adjacent to the "KLVFF" motif, Gly 25 is Hmb-substituted (see page 2020 peptide structure), because the Hmb-substituted glycine mimic phenylalanine (F), the Quibell's teaching meets the limitation set forth in the instant claim 27.

Since the above-mentioned Gly 25 Hmb-substituent has similar stereochemistry of said chain of the phenylalanine residue thereby allows for a β-strand interaction, the above Quibell' teachings anticipates the instant claim 28.

The applicant's response to the rejection under 35 USC 102

The response filed 18 October 2004 discusses the first edge and the second edge of the claimed peptide compound (pages 37-39), presents Figure 1 to illustrate the topological scheme

of said first and second edges, and infers that N-terminal and C-terminal regions reside oppositely along the claimed β-strand forming section. The applicants' argument is not persuasive because the instant disclosure does not specify the edges, and because (i) the Quibell's polypeptide structure indicated above meets the limitation, i.e., "a first edge and a second edge, corresponding to opposite sides of said peptide backbone" set forth in item *a* of claim 1, and (ii) moreover, the Figure 2 does not clearly demonstrate topological relation of these two edges.

In pages 39-42, the response also discusses (1) the issue regarding comparison of function/activity (e.g., inhibition of aggregation) of the Quibell's polypeptide compound with that of the instant compound peptide, and (2) involvement of Gly 37 residue in β-structure (β-turn) formation; the response infers that Quibell et al. do not disclose the peptide compound comprising a β-strand-forming section which has the two edges, one of which associates with a target β-strand, and one of which comprises at least four α-L-amino acids wherein at least one of said amino acids is Nα-substituted set forth in the claims (see page 42, the second paragraph).

The Applicants' argument is found to be unpersuasive because (i) the Quibell's polypeptide meets all the limitations set forth in claim 1 and the dependent claims (rejected) thereto (see the statement supra); (ii) N- and C-terminal regions of the Quibell's polypeptide meet the limitation "the two edges" even wherein "KLVFF" (residue 16-20) motif of the Quibell's polypeptide, which comprises one Nα-substitution (i.e., Hmb-Phe (F) 20); thus, Quibell et al. teach all structural features (limitations) set forth in the instant claims; and (iii) in the Quibell reference, Gly 37-Hmb substitution acts to improve quality (solubility) and overall yield of the polypeptide by reducing interchain interactions occurring between β-hairpin

structures in which Gly 37 residue (see conclusion and page 1995, the left col.); this thus would assist the polypeptide having "KLVFF" motif in preventing aggregation been β-amyloid like polypeptides. Note that the Quibell' composition is such polypeptide.

On page 38, the response discusses the issue regarding Nα-substituent, i.e., blocking groups in the β-strand forming section of the claimed peptide compound and its inability of association with other β-strand. The subsequence of the Quibell's polypeptide (KLVFF) comprises the blocking group, the last phenylalanine residue, which is Hmb-modified, i.e., Nα-substituted. The Hmb (blocking) group of said Nα-substituted phenylalanine resides on one edge (second) opposite to the other edge (first) of peptide backbone of said subsequence. The Quibell's polypeptide comprising the subsequence "KLVFF" is able to interact with target molecule, e.g., naturally-occurring β-amyloid that comprises said subsequence, *through* unmodified KLVF sequence, whereas the Hmb-modified phenylalanine (the second edge of the subsequence) blocks its association with other β-strand. Thus, the Quibell's teachings meet the description for the blocking groups in the second edge of β-strand forming section in Figure 2 of the response page 38. The applicant's argument is therefore is found to be unpersuasive.

It should be stressed that the "KLVFF" subsequence in the Quibell' polypeptide *per se* is qualified for being a prior art composition over the instant invention. Thus, the Quibell's polypeptide anticipates the current invention.

The following is a new ground of rejection

Claims 1, 4-18, 22-28 and 43 are rejected under 35 U.S.C. 102(e) as being anticipated by Kelly, J. W. (US Pat. No. 6034211) as is evidenced by the known fact that proteolysis-

resistance is an *inherent property* of the Nα-substituted polypeptide) disclosed in the reference by Miller S. M. et al. (*Drug Dev. Res.* (1995) 35, 20-32, provided by the IDS filed 18 October 2004).

In the patent claim 1, Kelly teaches a chemical compound, i.e., a β-sheet peptidomimetic comprising (i) the first peptide (*recognition strand*) of 3 to 21 amino acid residues which further comprises a recognition sequence that interacts with a target protein which self assembles (e.g., β-amyloid protein (see column 11, lines 37-43, and column 12), and (ii) a second peptide (*blocking strand*) of 3 to 21 amino acid residues which further comprises Nα-substituted residues, e.g., N-methylated residue. The kelly's compound has the structural characteristics of the composition of the instant claim 1, i.e., (1) the first peptide is able to associate with a target β-strand; (2) the first and the second peptides are β-forming sequences (see Scheme II depicted on columns 13-24) and N-methylated (see column 13, lines 18-20); (3) the said β-forming sequence comprises a subsequence wherein at least one in every 8 residues is N-methylated (see column 14, lines 1-3), and wherein the said residues are α-L-amino acids; and (4) the Kelly's patent is directed to an inhibitor of β-strand aggregation (see column 14, lines 25-40) which inhibits amyloid protein assembly (see column 23, lines 43-57). The Kelly's patent therefore anticipates the instant claim 1.

Please note that the above said the first and the second peptides are corresponding to the first edge and the second edge of the peptide of the instant application, respectively; and that in item *c* of claim 1, the recitation "at least one of which is substituted with an Nα-substituent" excludes the limitation set forth in item *d* of the claim, which requires (at least) two successive Nα-substituents thereof. Thus, the Kelly's patent is an anticipatory art over the current invention.

The Kelly's compound depicted in the Scheme II (columns 13-24) shows the said Nα-substituents allow β-strand formation, which anticipates the instant claims 4 and 7.

Since proteolysis-resistance is an inherent property of the said composition (i.e., compound comprising Nα-substituted polypeptide) as is evidenced by Miller et al. reference, the above Quibell et al. teachings are applied to the instant claim 5.

In the Kelly's compound, N-methylation is conjugation of a methyl group to Nα, which anticipates the instant claim 6.

The β-forming strand of the blocking strand of the Kelly's compound comprises valine, leucine and isoleucine (see the patent claim 1, item c), all of which have β-sheet formation propensity > 1.00, which anticipates the instant claim 8.

Kelly teaches that the first and the second peptide strands comprise β-strand forming sections which participate in non-covalent interaction, e.g., hydrophobic interaction (see column 11, the 4th paragraph), which anticipates the instant claims 9-10.

In the Scheme II (columns 17-22) show that Kelly's peptide compound comprises β-strand breaker lysine, i.e., propensity (Pr) of forming β-strand is less than 1 (lysine's Pr value = 0.74) (see attachment 1); hence, the kelly's teaching is applied to the instant claim 11.

In Figure 1 (*a*) Quibell et al. teach a neighboring side chain interaction in secondary structure of the β-forming polypeptide, which anticipates the instant claim 12.

In column 25, lines 31-37, Kelly et al. teach a radiolabled compound in order to allow the compound to be detectable, which anticipates the instant claim 13-14.

In the patent claim 1, Kelly et al. teach that the amino acid residues in the β-strand forming section are valine, leucine and isoleucine, which anticipates the instant claim 15.

Kelly teaches that the recognition strand of said compound interacts with a recognition sequence (i.e., target molecule) that comprises the core sequence: i.e., KLVFF (see SEQ ID NO:19, and column 11, line 62 to column 12, line 10) from naturally occurring β-amyloid, which anticipates the instant claims 16 and 26.

Since the target β-stand from Alzheimer's β-amyloid that comprises KLVF (SEQ ID NO:17, and see column 12, lines 1-7, and column 23, the left column, the last paragraph), which meets the limitation set forth in the instant claim 17.

Since the β-stand forming peptides of the Kelly's compound comprises 4 amino acid residues KIFY (Lys-Ile-Phe-Tyr) (see SEQ ID NO:13, and columns 17-18), which anticipates the instant claim 18.

The Kelly's β-structures depicted in Scheme II (columns 17-18) shows the structures have a free N-terminus and an amidated C-terminus, which anticipates the instant claim 22.

In the kelly's compound, the β-strand(s) is linked to a functional group, diarylheterocycle (see the patent claim 1 and the structures shown in Scheme II), which anticipates the instant claim 23.

Kelly teaches that the compound (a β-turn mimic) promotes interstrand interaction between said compound and target sequence (recognition sequence) in a highly favorable conformation for binding to the said target protein (see column 10, lines 1-17), which anticipates the instant claim 24.

In the Scheme II on columns 15-18, Kelly shows that the β-strand forming section of the compound is linked to the above mentioned functional group via an amide bond, which anticipates the instant claim 25.

On column 31, lines 12-14, Kelley teaches one component, i.e., phenylalanine which substitutes for leucine (note that the Pr value (*measuring propensity of forming β-strand*) Phe (1.38) is higher than Leu (1.30), see the attachment 1), indicating that the component-containing compound will mimic action of that of the peptide compound (comprising the leucine thereof), which anticipates the instant claim 27.

In the above stated compound, the leucine side chain is replaced by side chain of phenylalanine side chain, both side chain are non-polar and involving hydrophobic interaction, which meets the limitation set forth in the instant claim 28.

Additionally, Kelley teaches a pharmaceutical composition comprising the (patent) claimed compound (see column 24, the 2nd paragraph), which anticipates the instant claim 43.

The provisional rejection under 35 U.S.C. 101, Double Patenting, is withdrawn because the 1003138 application is directed to α-D-amino acids rather than α-L-amino acids.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu, Ph.D. whose telephone number is (571) 272-0949. The examiner can normally be reached Monday-Friday 9:00 -5:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber, can be reached on (571) 272-09525. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communication and (703) 305-3014 for the after final communication.

Samuel Wei Liu, Ph.D.
Art Unit 1653, Examiner
February 17, 2005

JON WEBER
SUPERVISORY PATENT EXAMINER